Long term follow-up of patients with coiled intracranial aneurysms
Sprengers, M.E.S.

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Chapter 1

General introduction, aims and outlines
Subarachnoid hemorrhage (SAH) from an intracranial aneurysm is a life-threatening disorder: about half of the patients die on direct impact of the hemorrhage, vasospasm or medical complications, one quarter survives with neurological deficits and only one quarter makes a good recovery. Directly after SAH, the most dangerous threat is an early recurrent hemorrhage, which is fatal in the majority of cases. To prevent this lethal recurrent hemorrhage, early securing of the aneurysm is needed.

In the last decades, new micro-neurosurgical techniques were developed to put a clip over the neck of the aneurysm. Thus, most aneurysms could be adequately clipped with a low complication rate. However, the risk of complications of aneurysm surgery increases with large aneurysm size, with aneurysm location in the posterior circulation and with patients in poor clinical condition. Some aneurysms could not or not timely be clipped and alternative endovascular approaches to treat these difficult aneurysms and patients were developed. With new micro catheters it became possible to catheterize intracranial aneurysms and the introduction of detachable coils allowed the operator to fill the aneurysm lumen with platinum coils to prevent recurrent hemorrhage. Soon after the introduction of coiling of intracranial aneurysms, it became clear that initial results were promising for inoperable aneurysms and indication was first extended to operable aneurysms in poor grade patients and later to all aneurysms that were suitable for coiling. In 2001, the results of a large randomized controlled study of clipping versus coiling (ISAT) showed that patients who were coiled had a better outcome than patients who were clipped. From then on, coiling gradually replaced surgery as the treatment of choice for intracranial aneurysms and clipping is only indicated in aneurysms not suitable for coiling. Although coiling has become the treatment of choice for both ruptured and unruptured intracranial aneurysms this technique has several shortcomings. Not all aneurysms can be occluded completely at first treatment, leaving the patient at risk for early recurrent haemorrhage in case of a recently ruptured aneurysm. Another drawback is the possibility of reopening with time of an initially adequately occluded aneurysm as a result of coil compaction, aneurysm growth or dissolution of an intraluminal thrombus. Reopening occurs in about 20% of coiled aneurysms and half of these aneurysms are retreated. The other half is not retreated because of the reopening is small, has an unfavourable geometry for additional coiling or retreatment is not judged indicated in the clinical context. Possible risk factors for reopening of a coiled aneurysm over time are large aneurysm size, presence of intra luminal thrombus, low packing density, initial incomplete occlusion, longer follow-up and a wide neck. From published data, the robustness and power of separate contribution of these risk factors remain obscure by differences in study design, aneurysm selection, and method of follow-up. As a consequence, it is unknown for how long and how often coiled aneurysms need to be followed and whether certain subgroups carry a higher or lower risk for reopening.

**Why do patients with coiled aneurysms need imaging follow-up?**

The most important reason for imaging follow-up is the fact that reopening after coiling is with 20% frequent. An incompletely occluded aneurysm exposes the patient to a risk for recurrent SAH on the long-term and retreatment is advocated.

The second reason for imaging follow-up is the increasing awareness that an aneurysm might be an expression of a general disease of the intracranial arteries and not a once in a lifetime event. Many patients presenting with an aneurysm have multiple aneurysms. With modern 3D imaging, these additional aneurysms are detected with increasing frequency. When possible, additional aneurysms are treated but many are not, mostly because of small size and presumably a low rupture risk. However, these small aneurysms can grow and since the risk of rupture increases with size,
prolonged imaging follow-up is advocated to detect growth. In addition, on diseased intracranial arteries new aneurysms can develop later in time that can also become a source of recurrent SAH.

Little is known about the pace of growth of untreated additional aneurysms and the frequency and timing of development of new aneurysms, and thus for need for and timing of long-term imaging follow-up for these aneurysms.

**Timing of reopening of coiled aneurysms and implication for timing of follow-up**

An important issue is the timing of occurrence of reopening after coiling. Do all reopenings develop within the first 6 months or can aneurysms still reopen after a longer period of stable adequate occlusion? Or, can an aneurysm that is adequately occluded at 6 months still reopen at a later point in time and if yes, at what point in time?

The results of follow-up studies to date are not conclusive. The discrepancies of conclusions are confusing in clinical practice: if more reopenings are found with longer follow-up, prolonged imaging follow-up would be mandatory to detect these late-onset reopenings. On the other hand, if adequately occluded aneurysms at 6 months do not reopen later, extended follow-up is not necessary.

**Imaging modalities for follow-up**

The standard imaging modality for the mandatory follow-up is catheter angiography. This is an invasive imaging technique that provides high resolution images at the expense of a small risk of serious neurological complications. Magnetic Resonance Angiography (MRA) has evolved as an alternative non-invasive imaging modality to assess occlusion status of coiled intracranial aneurysms, possible growth of untreated intracranial aneurysms and development of any new aneurysms with promising, but not yet conclusive results. MRA can be performed without contrast enhancement with 3D time-of-flight (TOF-MRA) or with contrast enhancement (CE-MRA). Contrast administration has several disadvantages such as patient discomfort, risk of renal damage, risk of allergic reaction and higher costs. Currently, different MRA techniques are evaluated to establish whether non-invasive MRA can replace invasive angiography in the follow-up of coiled intracranial aneurysms.

In this thesis, different MRA techniques to follow coiled intracranial aneurysms are evaluated and compared to angiography. In addition, MRA is used for long-term follow-up of coiled intracranial aneurysms to evaluate occlusion stability and to possible identify subgroups of patients that do not need extended imaging follow up.
Aims and outline

In Chapter 2 we assessed the feasibility and diagnostic value of 3D time-of-flight (TOF) MRA at 3T compared with angiography for the follow-up of coiled intracranial aneurysms. Twenty patients with 21 coiled aneurysms underwent both contrast enhanced (CE) MRA and non-enhanced TOF-MRA at 3T six month after coiling.

In Chapter 3 we compared TOF-MRA and CE-MRA at 3Tesla with angiography to asses the diagnostic accuracy in the assessment of the occlusion status of coiled intracranial aneurysms. Anonimized TOF-MRA and CE-MRA images at 3T of 67 patients with 72 aneurysms were evaluated and compared with angiography as standard reference test.

In Chapter 4 we conducted a systematic review and meta-analysis of 42 selected studies reporting on initial occlusion, reopening, and retreatment rates of coiled intracranial aneurysms.

In Chapter 5, we performed a multi-center long-term imaging follow-up study with 3T TOF-MRA. One-hundred-and-four patients with 111 coiled aneurysms adequately occluded on the 6 months follow-up angiogram underwent TOF-MRA 5-11 years after coiling, to assess the stability of occlusion and the long-term. Incidence and therapeutic consequences of long-term reopening were evaluated.

In Chapter 6, we used TOF-MRA to assess the incidence of de novo aneurysm formation and determine the natural history of additional untreated aneurysms in 65 patients with coiled intracranial aneurysms after a fixed follow-up period of 5 years.

In Chapter 7 we used TOF-MRA to assess the incidence of de novo aneurysm formation and the occurrence of enlargement of existing untreated aneurysms in patients with aneurysms treated with therapeutic carotid artery balloon occlusion. In addition, we assessed the incidence of SAH during an average follow-up period of 50.3 months.

In Chapter 8 we report the incidence, imaging- and clinical characteristics of patients with aneurysms that repeatedly reopened over time and were treated three times or more for the same aneurysm with emphasis on clinical outcome during extended follow up of 2-11 years.

In Chapter 9 we assessed the long-term cumulative incidence of recurrent SAH in patients with coiled aneurysms that were adequately occluded at 6 months. This cumulative incidence was compared to the long-term recurrent SAH after clipping.

In Chapter 10 we compared 3D rotational angiography (3DRA) with conventional angiography in the depiction of small additional aneurysms.

Finally, in Chapter 11, the main findings of our studies are summarized and discussed.